*Investigation vignette*

# A 37 Year old Man with Intermittent Abdominal Pain and a Non-Lactic, Non-Ketone, High Anion Gap Metabolic Acidosis

**CASE REPORT**

A 37 year old man was admitted to the accident and emergency department complaining of intermittent abdominal pain and malaise for one month with nausea and vomiting for the past 3 days. His past medical history was unremarkable and his only medication was paracetamol.

On examination he was in sinus rhythm at a rate of 72 beats per minute, respiratory rate 28 per minute, temperature was 35.8°C and a blood pressure of 100/80 mmHg. On examination he had a soft abdomen with slight tenderness in the right upper quadrant with no guarding or rebound tenderness. No other abnormalities were found.

A central venous cannula was inserted into the right subclavian vein and an arterial cannula was inserted into the right radial artery. The patient was resuscitated with 2 litres of 0.9% saline intravenously during the first 2 hours and one litre of 5% dextrose with 60 mmol of potassium chloride over the next 6 hours.

The plasma biochemistry on admission revealed a sodium of 137 mmol/L, potassium 3.4 mmol/L, bicarbonate 9 mmol/L and amylase of 110 U/L. The haemoglobin was 135 g/L and the white cell count was 8.2 x $10^9$/L. The arterial blood gases revealed a $PO_2$ of 110 mmHg, $PCO_2$ 12 mmHg and pH 7.24. The anion gap was 31.4 mEq/L, plasma lactate 1.1 mmol/L, acetoacetate 0.09 mmol/L and beta-hydrox-ybutyrate 0.22 mmol/L. The plasma biochemical results during the first two days of treatment are shown in figure 1.

| Name | Age | Sex |
|---|---|---|
| Mr. D. D. | 37 | M |

| | **21/12** | **22/12** | **23/12** | | |
|---|---|---|---|---|---|
| Sodium | 137 | 139 | 135 | mmol/L | (135 - 145) |
| Potassium | 3.4 | 3.4 | 3.6 | mmol/L | (3.2 - 4.3) |
| Chloride | 100 | 109 | 106 | mmol/L | (99 - 109) |
| Bicarbonate | 9 | 17 | 22 | mmol/L | (22 - 32) |
| Anion gap | 31.4 | 6.4 | 10.6 | mEq/L | (8 - 16) |
| Creatinine | 0.13 | 0.06 | 0.6 | mmol/L | (0.05 - 0.12) |
| Glucose | 7.8 | 6.5 | 5.7 | mmol/L | (3.5 - 5.4) |
| LDH | 213 | 168 | 132 | U/L | (105 - 230) |
| ALT | 238 | 124 | 90 | U/L | (< 40) |
| AST | 213 | 38 | 27 | U/L | (< 45) |
| $PO_2$ | 110 | 88 | 87 | mmHg | (80 - 105) |
| $PCO_2$ | 12 | 25 | 29 | mmHg | (35 - 45) |
| pH | 7.24 | 7.39 | 7.45 | | (7.35 - 7.45) |
| BE | -19 | -8 | - 4 | mmol/L | (-3 - + 3) |
| Lactate | 1.1 | 0.9 | 1.2 | mmol/L | (< 2.0) |

**Figure 1**. Blood gases and plasma biochemical results on admission and during the next two days in the intensive care unit

**Diagnosis: Pyroglutamic acidosis due to paracetamol toxicity.**

As the patient admitted to taking up to 8 g of paracetamol daily for the three weeks prior to his admission, a serum paracetamol level was measured which recorded a level of 790 μmol/L. Subsequently, urinary electrophoresis and gas chromatography revealed a high pyroglutamic acid level.

Following his initial intravenous fluid resuscitation he was treated with intravenous N-acetyl cysteine (10 g over 15 min followed by 3 g in 4 h, followed by 10.5 g in 24 h for three days). Fluid therapy consisted of two litres of 4% dextrose and 0.18% saline with 60 mmol of potassium chloride daily for 48 hours. Sodium bicarbonate was not administered.

Unlike other reported cases of pyroglutamate acidosis,[1] the patient was not septic and did not have a severe systemic inflammatory response to his disorder. Twenty fours after admission the serum paracetamol level was < 5 μmol/L.

Paracetamol toxicity usually causes a high anion gap metabolic acidosis due to a lactic acidosis.[2] However, a high anion gap metabolic acidosis with normal lactate and ketone levels has also been reported in paracetamol toxicity due to pyroglutamic acidosis.[3-5] The diagnosis is made by detecting a high anion gap metabolic acidosis (not explained by an elevated plasma lactate, beta-hydroxybutyrate, acetoacetate, citrate, formate, salycilate, amino-acids or albumin) and detecting pyroglutamate (5-oxoproline) acidaemia or aciduria. Pyroglulamate aciduria has also been described as a rare inherited metabolic disorder presenting in infancy, in children taking vigabatrin[6] and in an adult patient with staphylococcal pneumonia taking flucloxacillin and netilmicin.[7]

Paracetamol toxicity (particularly in the presence of sepsis and glutathione depletion) causes a reversible inhibition of either glutathione synthetase or 5-oxoprolinase, increasing pyroglutamate levels due to an overproduction (secondary to inhibition of glutathione synthetase) or reduction in breakdown (due to inhibition of 5-oxoprolinase) of pyroglutamate.[1]

The normal minimal threshold dose of paracetamol in an adult is 10 g before glutathione availability is exceeded,[8,9] although in malnourished patients and following starvation, toxicity may occur after ingestion of 4 - 10 g of paracetamol.[10]

As well as the acidosis the patient also had biochemical evidence of hepatic injury with an elevated ALT, AST and LDH (although all were less than 1000 U/L). Renal insufficiency was also recorded on admission (e.g. creatinine 0.13 mmol/L) although this was probably a pre-renal effect as the blood pressure and urine output increased and creatinine decreased rapidly with intravenous fluid therapy.

Standard therapy for paracetamol toxicity is intravenous N-acetylcysteine to enhance and replenish glutathione stores by acting as a precursor for glutathione synthesis,[11,12] although N-acetylcysteine may also have direct antioxidant effects by acting as a glutathione substitute or even enhancing nontoxic sulphate conjugation of paracetamol.[13]

The acidosis, hepatic dysfunction and abdominal pain resolved over three days and the patient was discharged from the intensive care unit and has been symptom free for the last 2 months.

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REFERENCES

1. Dempsey GA, Lyall HJ, Corke CF, Scheinkestel CD. Pyroglutamic acidemia: a cause of high anion gap metabolic acidosis. Crit Care Med. 2000;28:1803-1807.
2. Gray TA, Buckley BM, Vale JA. Hyperlactataemia and metabolic acidosis following paracetamol overdose. Q J Med 1987;65:811-121.
3. Creer MH, Lau BW, Jones JD, Chan KM. Pyroglutamic acidemia in an adult patient. Clin Chem 1989;35:684-686.
4. Pitt JJ, Hauser S. Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. Clin Chem 1998;44:1497-1503.
5. Pitt JJ, Brown GK, Clift V, Christodoulou J. Atypical pyroglutamic aciduria: possible role of paracetamol. J Inherit Metab Dis 1990;13:755-756.
6. Bonham JR, Rattenbury JM, Meeks A, Pollitt RJ. Pyroglutamicaciduria from vigabatrin. Lancet 1989;i:1452-1453.
7. Croal BL, Glen AC, Kelly CJ, Logan RW. Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult receiving antibiotic therapy. Clin Chem 1998;44:336-340.
8. Prescott LF. Hepatotoxic dose of paracetamol. Lancet 1977;ii:142.
9. Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Kieser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974;16:676-684.
10. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol abuse. JAMA 1994;272:1845-1850.
11. Beatty P, Reed BJ. Influence of cysteine upon the glutathione status of isolated rat hepatocytes. Biochem Pharmacol 1981;30:1227-1230.

12. Meredith TJ, Prescott LF, Vale JA. Why do patients still die from paracetamol poisoning? Br Med J 1986;293:345-346.
13. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the National Multicenter Study. N Engl J Med 1988;319:1557-1562.